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EXAMINER	
BERTAGNA, ANGELA MARIE	
ART UNIT	PAPER NUMBER
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/28/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/757,263	WANG, XIAO B.	
	Examiner	Art Unit	
	Angela Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-19,23-33 and 44-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4-19, 23-33, 44-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Applicant's response filed October 18, 2006 is acknowledged. Claims 1, 2, 4-19, 23-33, and 44-48 are currently pending. Claims 1, 2, 44, 47 and 48 were amended, and claims 3 and 20-22 were canceled in the response. This action is made non-final due to the inclusion of new grounds of rejection not necessitated by Applicant's amendment (double patenting rejection).

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120. The later-filed application must be an application for a patent for an invention that is also disclosed in the prior application (the parent or original non-provisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosures of the prior-filed applications, Application No. 09/862,417 (now USPN 6,824,980) and Provisional Application 60/209,987, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Specifically, the prior-filed applications do not provide support for hybridizing the equal-length extension products generated in the first hybridization reaction with a second primer and conducting a second primer extension reaction. Therefore, the examined

claims (1-33 and 44-48) have not been granted benefit of the earlier filing date of the above applications (09/862,417 & 60/209,987), and the instant application filing date of January 14, 2004 has been used as the effective filing date.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 1, 2, 4-19, 23-33, and 47 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Oliphant et al. (US 2003/0108900 A1; newly cited).

Regarding claim 1, Oliphant teaches a method (see, for example, Figure 3) for detecting or quantifying a known target polynucleotide having a known nucleotide sequence comprising:

(a) hybridizing a first primer to a specific region of the known target polynucleotide and extending the first primer using one to three of four types of non-terminator nucleotides selected from A, T or U, G, and C to produce equal length primer extension products, wherein the extended portion of the first primer comprises one to three of four types of nucleotides (Figure 3, step 1 and paragraph 352; paragraph 151 teaches that a single non-terminator nucleotide can be added in the extension reaction; see also paragraph 156)

(b) hybridizing the equally extended portion of the first primer to a second primer, wherein the second primer comprises a region complementary to the equally extended portion of the first primer (Figure 3, step 3 and paragraphs 352-353, where the second primer is hybridized to the first extension product)

(c) producing extension products from the second primer (Figure 3, step 3 and paragraphs 352-353)

(d) detecting the extension products from the second primer (paragraph 353).

Regarding claim 2, in the method of Oliphant described above, the extension products of the first primer comprise a primer portion and an extended portion and the extended portion comprises one to three of the four types of nucleotides (see Figure 3 and paragraphs 352-353).

Regarding claim 4, the second primer of Oliphant is not complementary to the first primer (see Figure 3, where the second primer hybridizes to the extended portion of the first primer extension product rather than the primer portion).

Regarding claim 5, in the method of Oliphant, the amount of detectable extension product correlates to the amount of target polynucleotide (paragraphs 353 and 442).

Regarding claim 6, Oliphant teaches annealing of the first and second primers under high stringency (paragraph 17).

Regarding claim 7, Oliphant teaches that the extension products from the second primer are detected using mass spectroscopy (paragraph 387) or fluorescence spectroscopy (paragraph 400).

Regarding claims 8 and 9, Oliphant teaches that the products from the second primer extension contain a detectable label (paragraph 353), such as a fluorophore, an eptiope, an

enzyme, a polypeptide, a carbohydrate, a radioactive isotope, a dye, or biotin (paragraphs 96 and 337-341)

Regarding claims 10 and 11, Oliphant teaches that the primers and target nucleic acid comprise DNA or RNA (paragraphs 35 and 40).

Regarding claims 12-14, Oliphant teaches enzymatic production of extension products using the template-dependent enzyme DNA polymerase (see Figure 3 and paragraph 348).

Regarding claims 15-19, Oliphant teaches enzymatic synthesis of the target nucleic acid by PCR (paragraph 41). Oliphant also teaches that the target nucleic acid may comprise genomic DNA, mRNA, or cDNA (paragraph 40). Oliphant further teaches that the target nucleic acid may be obtained from humans or mammals (which are vertebrates), bacteria or viruses (paragraph 31).

Regarding claims 23 and 25, Oliphant teaches that the first primer comprises one or more moieties that permit affinity separation of the primer from unincorporated reagent and/or the polynucleotide of interest (see Figure 3, where the first primer is biotinylated).

Regarding claims 24 and 25, Oliphant teaches that the second primer comprises one or more moieties that allow immobilization of the second primer onto a solid support to produce an immobilized second primer sequence (paragraph 354 teaches that the second primer is labeled; paragraphs 337-341 teach detectable labels include attachment moieties such as biotin).

Regarding claims 26 and 27, Oliphant teaches that the second primer is synthesized directly (via chemical synthesis) on a solid support to produce an immobilized second primer sequence (paragraph 337 teaches labeling with a nanocrystal – a solid support).

Regarding claim 28, Oliphant teaches that the first primer is immobilized onto a solid support to produce an immobilized target nucleic acid sequence (paragraph 354).

Regarding claims 29 and 30, Oliphant teaches that the first primer can be cleaved from the solid support by a chemical process, specifically via cleavage of a photocleavable bond (paragraphs 84 and 85 teach immobilization of primers on a solid support or array; paragraph 403 teaches photolithographic production of the array).

Regarding claim 31, Oliphant teaches that the solid support comprises beads or flat surfaces (paragraphs 84 & 85).

Regarding claim 32, Oliphant teaches that the immobilization of the first primer is accomplished by hybridization between a complementary capture nucleic acid molecule, which has been previously immobilized to a solid support (paragraphs 56-59).

Regarding claim 33, Oliphant teaches that immobilization is accomplished via direct bonding between the solid support and a portion of the nucleic acid molecule, which is distinct from the target nucleic acid sequence (paragraphs 87-90).

Regarding claim 47, Oliphant teaches a method to assist in diagnosing cancer in a host comprising:

(a) obtaining from the host a sample comprising a polynucleotide (paragraph 31);

(b) contacting the sample with a first primer, the first primer comprising a nucleotide sequence complementary to a portion of a known target polynucleotide (Figure 3, step 1 and paragraph 352), wherein the known target polynucleotide is an oncogene or variation thereof involved in or related to cancer (paragraph 4 teaches application of the method to oncogenes)

(c) extending the primer using a non-terminator nucleotide mixture formulated to produce equal length primer extension products (Figure 3, step 1 and paragraph 352; paragraph 151 teaches that a single non-terminator nucleotide can be added in the extension reaction; see also paragraph 156)

(d) hybridizing the equal length extension products to a second primer, wherein the second primer comprises a region for hybridizing to the first primer consisting of one to three types of nucleotides selected from the group consisting of A, T or U, C and G (Figure 3, step 3 and paragraphs 352-353, where the second primer is hybridized to the first extension product)

(e) producing extension products from the second primer (Figure 3, step 3 and paragraphs 352-353)

(f) detecting the extension products from the second primer (paragraph 353), wherein the detection of an extension product from the second primer is indicative of cancer or a predisposition to cancer.

Regarding the "wherein" clause in step (f) above, MPEP 2111.04 states, "a 'whereby clause' in a method claim is not given weight when it simply expresses the intended result of a process step positively recited." Here, the application of the above method taught by Oliphant to oncogenes (also taught by Oliphant) inherently results in the intended result stated in the "wherein" clause. Therefore, Oliphant anticipates claim 47.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oliphant et al. (US 2003/0108900 A1; newly cited) in view of Wang (EP 1 162 278 A2; cited previously).

Oliphant teaches a method of detecting a target polynucleotide comprising multiple primer extension steps (see Figure 3 and paragraphs 352-354).

Regarding claim 44, Oliphant teaches a method comprising:

(a) hybridizing a first primer to the target polynucleotide (Figure 3, step 1 and para. 352)

(b) forming equal length primer extension products using one to three of four types of non-terminator nucleotides selected from A, T or U, G, and C to produce equal length primer extension products, wherein the extended portion of the first primer comprises one to three of four types of nucleotides (Figure 3, step 1 and paragraph 352; paragraph 151 teaches that a single non-terminator nucleotide can be added in the extension reaction; see also paragraph 156)

(c) hybridizing the extended portion of the first primer to a second primer, wherein the second primer comprises a region complementary to the extended portion of the first primer consisting of one to three types of nucleotides selected from the group consisting of A, T or U, G, and C (Figure 3, step 3 and paragraphs 352-353, where the second primer is hybridized to the first extension product)

(d) extending the second primer with at least one nucleotide having a detectable marker using a portion of the extension products of step (b) as a template (Figure 3, step 3 and paragraphs 352-353)

(e) correlating the amount of detectable marker in the extension products of (d) with the amount of target polynucleotide (paragraphs 353 and 442).

Regarding claim 45, the second primer of Oliphant hybridizes to the non-primer portion of the first extension product (see Figure 3, where the second primer hybridizes to the extended portion of the first primer extension product rather than the primer portion).

Regarding claim 46, a primer portion of the first extension product serves as a template for extending the second primer (see Figure 3).

Oliphant does not teach that the mixture of non-terminator nucleotides consists of X, Y, and Z, where X and Y are different purine non-terminator nucleotides and Z is a pyrimidine non-terminator nucleotide. Oliphant also does not teach the mixture of non-terminator nucleotides consists of X, Y, and Z, where X and Y are different pyrimidine non-terminator nucleotides and Z is a purine non-terminator nucleotide.

Wang teaches an isometric primer extension method (see abstract). The method of Wang comprises the following steps: (a) hybridizing a primer to a target nucleic acid, (b) extending the primer using a mixture of one to three non-terminator nucleotides, and (c) detecting the resulting extension products by mass spectroscopy (page 2, paragraph 8).

Regarding claim 44, Wang teaches a set of nucleotides for primer extension consisting of two purine non-terminator nucleotides and one pyrimidine non-terminator nucleotide (page 3, mixture e, where dATP, dGTP and dCTP are taught). Wang also teaches a set of nucleotides for

primer extension consisting of two pyrimidine non-terminator nucleotides and one purine non-terminator nucleotide (page 3, mixtures b, d, f, and h).

Wang teaches that these mixtures generate extension products of a discrete length, thereby permitting a more accurate quantification of the target nucleic acid (page 3, paragraphs 16 & 17).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to use one of the mixtures of nucleotides taught by Wang in the method of Oliphant. Wang taught that the mixtures of three non-terminator nucleotides produced primer extension products of a discrete size, thereby permitting a more accurate quantification of target nucleic acids (see page 3, paragraphs 16-17). An ordinary practitioner of the method taught by Oliphant would have been motivated by these teachings of Wang to use such a mixture in the first extension reaction in order to better control the length of the resulting extension products, and thereby improve the accuracy of the genotyping results obtained. An ordinary practitioner would have been further motivated to use the nucleotide mixtures taught by Wang, because Oliphant taught that the composition of the nucleotide mixture could be altered to control the length of the extension products (paragraphs 151 and 156). Therefore, an ordinary practitioner of the method taught by Oliphant, interested in obtaining an increased level of control over the length of the primer extension products, would have been motivated to use one of the mixtures of non-terminator nucleotides taught by Wang, thus resulting in the instantly claimed methods.

7. Claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Oliphant et al. (US 2003/0108900 A1; newly cited) in view of Robertson et al. (Trends in Genetics (2000) 16(6): 265-271; newly cited).

Oliphant teaches the method of claim 47, as discussed above.

Oliphant teaches application of the mutation detection method to oncogenes (paragraph 4), but does not teach specific examples of oncogenes or other cancer-related target sequences.

Robertson teaches that mutations in receptor tyrosine kinases (RTKs) are linked to heritable cancer susceptibility (see abstract, page 265, column 2, and page 267, column 1).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to apply the method taught by Oliphant to mutation detection in RTKs. Robertson expressly taught that mutations in RTKs were linked to cancer susceptibility and further suggested that "many novel mutations remain to be identified (see abstract, page 265, column 2, and page 267, column 1). An ordinary practitioner of the method taught by Oliphant would have been motivated by these teachings of Robertson to apply the method to analysis of RTKs in order to identify novel and/or known mutations in RTKs associated with increased cancer susceptibility, thereby increasing the diagnostic applications of the method. Since Oliphant taught that virtually any target from any sample could be used in the method (paragraph 31), an ordinary practitioner would have expected a reasonable level of success in applying the method taught by Oliphant to RTK targets. Therefore, the method of claim 48 is obvious in view of the combined teachings of Oliphant and Robertson.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 4, 5, 7-19, 23-33 and 44-46 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5-10, 13-28, and 32-38 of U.S. Patent No. 6,824,980 B2 in view of Oliphant et al. (US 2003/0108900 A1).

The instant claims are drawn to a method comprising primer extension with a mixture of up to three non-terminator nucleotides to produce a first primer extension product followed by a second round of primer extension using the first extension product as a template. The claims of the '980 patent recite identical or more specific limitations of the instant claims with the exception that the '980 patent does not recite a second primer extension step. Specifically, claims 1 and 36 of the '980 patent recite the limitations of the instant claims 1, 2, 5, 7, and 44, again with the exception that the '980 patent does not recite a second primer extension step. The

limitations of the instant claims 10-16 are recited in claims 2, 3, and 6-10 of the '980 patent. The limitations of the instant claims 17-19 are recited in claims 13-17 of the '980 patent. The limitations of the instant claims 23, 25, 28-33 are recited in claims 20-28, 32-34 and 38 of the '980 patent.

Oliphant teaches the method of claims 1, 2, 4-19, 23-33 and 47, as discussed above. Regarding the second primer extension step, Oliphant states, "The second hybridization and extension step provides allele discrimination and an additional level of locus specificity prior to signal amplification (Figure 3)."

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to include a second primer extension step in the method recited in the '980 patent. An ordinary practitioner would have been motivated to do so, because Oliphant taught that this "provides allele discrimination and an additional level of locus specificity prior to signal amplification (Figure 3)." Therefore, the combination of the claims of the '980 patent and the teachings of Oliphant render the method of the instant claims an obvious variant.

Response to Arguments

9. Claim Objections

Applicant's arguments, see page 13, filed October 18, 2006, with respect to the objection to claim 46 have been fully considered and are persuasive. Applicant's amendment overcomes the objection, and therefore, it has been withdrawn.

Rejections under 35 U.S.C. 112, 1st paragraph

Applicant's arguments, see pages 15-16, filed October 18, 2006, with respect to the rejection of claims 47 and 48 as lacking enablement under 112, 1st paragraph have been fully considered and are persuasive. Applicant's amendment overcomes the rejection, and therefore, it has been withdrawn.

Rejections under 35 U.S.C. 112, 2nd paragraph

Applicant's arguments, see page 18, filed October 18, 2006, with respect to the rejection of claims 6, 9-11, and 24 as indefinite under 112, 2nd paragraph have been fully considered and are persuasive. Applicant's amendments overcome the rejections, and therefore, they have been withdrawn.

Rejections under 35 U.S.C. 102

Applicant's arguments, see page 20, filed October 16, 2006, with respect to the rejection of claims 1-33, 47, and 48 as anticipated by Koster have been fully considered and are persuasive. Koster does not teach all of the elements of the amended claims 1 and 47 (specifically, Koster does not teach using a mixture of one to three non-terminator nucleotides), and therefore, the rejection has been withdrawn.

Rejections under 35 U.S.C. 103

Applicant's arguments with respect to claims 44-46 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is 571-272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Angela Bertagna
Examiner, Art Unit 1637
December 20, 2006

amb

JEFFREY FREDMAN
PRIMARY EXAMINER
12/4/06